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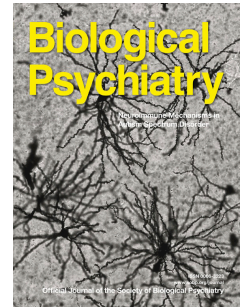
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Associations Between Non-Neurological Autoimmune Disorders and Psychosis: A Meta-Analysis

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ABSTRACT

BACKGROUND: A relationship between non-neurological autoimmune (NNAI) disorders and psychosis has been widely reported, but not yet subjected to meta-analysis. We conducted the first meta-analysis examining the association between NNAI disorders and psychosis, and investigated the effect of (a) temporality (as determined by study design), (b) psychiatric diagnosis, and (c) specific autoimmune disorders.

METHODS: Major databases were searched for articles published until April 2018. Thirty-one studies, comprising data for >25 million individuals, were eligible. Using random effects models, we examined the overall association between all NNAI disorders and psychosis, rheumatoid arthritis was examined separately given the well-established negative association with psychosis. Stratified analyses investigated the effect of temporality, psychiatric diagnosis, and specific NNAI disorders.

RESULTS: We observed a positive, overall association between NNAI disorders and psychosis (odds ratio = 1.26; 95% CI: 1.12 - 1.41) that was consistent across study designs and psychiatric diagnoses; however, considerable heterogeneity was detected ($I^2 = 88.09$). Patterns varied across individual NNAI disorders; associations were positive for pernicious anaemia (1.91; 1.29 - 2.84), pemphigoid (1.90; 1.62 - 2.24), psoriasis (1.70; 1.51 - 1.91), coeliac disease (1.53; 1.12 - 2.10), and Graves' disease (1.33; 1.03 - 1.72), and negative for ankylosing spondylitis (0.72; 0.54 - 0.98) and rheumatoid arthritis (0.65; 0.50 - 0.84).

CONCLUSIONS: Whilst we observed a positive, overall association between NNAI disorders and psychosis, this was not consistent across all NNAI disorders. Specific factors, including distinct inflammatory pathways, genetic influences, autoantibodies targeting brain proteins, or exposure to corticosteroid treatment, may therefore underlie this association.

INTRODUCTION

Findings from studies conducted over the past six decades have been used to support the claim that a relationship exists between non-neurological autoimmune disorders (NNAI, i.e., those largely affecting peripheral systems) and psychosis. In the 1950s, it was first observed that rheumatoid arthritis was less common among individuals with psychosis than in the general population (1, 2). Conversely, subsequent studies reported that other NNAI disorders, including coeliac disease, systemic lupus erythematosus, and autoimmune thyroid disorders, were more prevalent among individuals with psychosis (3-6). The most convincing evidence has come from several large-scale population studies which have demonstrated positive associations between schizophrenia and a range of autoimmune disorders (7-9). Whilst there has been increased interest in this topic in light of evidence of altered immune system function in psychosis (10-12), the overall association between NNAI disorders and psychosis has yet to be investigated using meta-analytic techniques.

Quantifying the degree of association between NNAI disorders and psychosis, and the extent to which this varies across study designs, specific psychiatric diagnosis, and individual NNAI disorders, may help to elucidate the mechanisms that underlie any relationship and ultimately lead to the identification of more effective intervention strategies. Disentangling the temporal nature of this relationship is an important first step to determining whether these disorders simply co-occur more commonly than expected, or whether NNAI disorders in fact increase the risk for psychosis. To this end, our study aimed to conduct the first meta-analysis examining the association between NNAI disorders and psychosis. Only NNAI disorders were included due to the well-established psychiatric manifestations of neurological autoimmune disorders. In the primary analysis, we examined effect sizes obtained from all studies irrespective of design or diagnostic outcome; however, given the well-documented negative

association between rheumatoid arthritis and psychosis, effect sizes for this disorder were examined in isolation. Stratified analyses were conducted to further examine the extent to which (a) temporality (as determined by study design), (b) specific psychiatric diagnoses (schizophrenia vs. more broadly defined psychosis vs. non-schizophrenia psychosis), and (c) specific NNAI disorders, influenced the magnitude and consistency of any effect.

METHODS AND MATERIALS

Search Strategy

As far as possible, the search strategy was conducted in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (13), as detailed in Supplementary Table S1. In brief, PubMed, PsycINFO, EMBASE, WorldCat dissertations and Theses, and Global Health were searched for all articles published until April 2018, with reference lists of review articles manually searched. Searches included the terms “psychosis” or “schizophrenia” or “non-affective psychosis” or “clinical psychotic symptoms” combined with “autoimmune disorders” or “autoimmune diseases” or “XXX”, the latter representing 37 individual NNAI disorders (see Supplementary Table S2). Autoimmune disorders included in the search strategy were selected *a priori* from the American Autoimmune and Related Diseases Association [AARDA (14)] all disorders were cross-checked against known neurological disorders, as listed by the American Academy of Neurology (15), and only those that did not appear here were deemed eligible for inclusion. Full texts of articles were retrieved as necessary and study authors were contacted where these were unavailable.

Selection Criteria

Detailed inclusion and exclusion criteria are provided in Supplementary Table S3. After a preliminary screen (title and abstract) to exclude studies that clearly did not meet eligibility

criteria, two of the authors (A.E.C and S.H.) reviewed the full text of all potentially eligible studies to determine inclusion. Disagreements were resolved by discussion with all study authors.

Data Extraction

Two researchers (A.E.C and S.H.) independently extracted information on year of publication, psychiatric diagnosis, autoimmune disorders, country, study design, data source, sample size, mean or median age of sample, participant sex, matching factors, and outcome measure (prevalence or incidence). To examine the effect of temporality, all eligible studies were categorised as follows: (1) studies examining the comorbidity of NNAI disorders and psychosis (type A); (2) studies in which the autoimmune disorder preceded the onset or measurement of the psychotic disorder (type B); and (3) studies in which the psychotic disorder preceded the onset or measurement of the autoimmune disorder (type C).

We included studies providing prevalence or incidence data on the basis that psychotic and autoimmune disorders are both rare, thus odds and risk ratios are likely comparable (16). To pool data across studies reporting different effect size measures, we extracted raw data from all eligible studies as follows: the number of individuals with both psychosis and an autoimmune disorder (a), the number of individuals with psychosis who did not have an autoimmune disorder (b), the number of individuals without psychosis who had an autoimmune disorder (c), and the number of individuals who had neither psychosis nor an autoimmune disorder (d). Extracted data were used to compute odds ratios $((a/c)/(b/d))$ with 95% confidence intervals; a continuity correction of 0.5 was applied to cells with zero counts (17). Thus, our pooled effect sizes represent raw (unadjusted) associations.

Where the stated aim of the study was to examine 'autoimmune disorders', and efforts were made by the authors to distinguish these from similar disorders with other (non-autoimmune) causes, we extracted data for all disorders classified as autoimmune by the authors (excepting those with a neurological basis); this included various forms of anaemia (8, 9, 18). For studies reporting data for both schizophrenia and more broadly defined psychosis (where the latter included schizophrenia) we subtracted schizophrenia cases from the total number of psychosis cases to obtain mutually exclusive groups. Where studies examined multiple NNAI disorders and/or more than one psychiatric outcome, data were extracted for each NNAI disorder/psychiatric outcome separately such that a single study could provide multiple effect sizes. Authors were contacted when these data were not reported in the publication, with data provided for some studies (4, 18-22), but not others (7, 23-25).

Eligible studies were assessed for quality by the first author (A.E.C.) using a modified version of the Newcastle-Ottawa Scale [NOS (26)]. The NOS provides separate assessment criteria for cross-sectional, case-control, and cohort studies, covering three methodological domains (selection criteria, comparability, and measurement of exposure/outcome). Scoring criteria were amended such that the maximum score available for each study design was eight (see Supplementary Table S4).

Statistical Analyses

Meta-analyses were conducted using Comprehensive Meta Analysis Software version 3.0. Given that the studies varied with respect to design and specific autoimmune disorders examined, we anticipated that the 'true effect' would vary across studies; all analyses were therefore conducted using a random-effects model with inverse weighting applied (27). Stratified analyses were used to explore potential mechanisms and sources of heterogeneity.

We first examined the overall association between NNAI disorders and psychosis, excluding effect sizes pertaining to rheumatoid arthritis. Next, we explored the effect of temporality by conducting analyses for each of the separate study design types defined above (A, B, and C). In the third step, we stratified by psychiatric diagnosis to determine whether the association with autoimmune disorders varied according to whether the outcome was schizophrenia, more broadly defined psychosis (including schizophrenia), or non-schizophrenia psychosis. Finally, meta-analyses were conducted for individual autoimmune disorders where more than three effect sizes were available. Statistical significance was set at $P < 0.05$ (2-tailed) for all analyses. Heterogeneity was assessed via the Cochran Q statistic (to identify statistically significant heterogeneity) and the I^2 statistic (to estimate the percentage of the variability in odds ratios due to heterogeneity) where classification of the latter as likely 'unimportant' (0-40%), 'moderate' (30-60%), 'substantial' (50-90%), or 'considerable' (75-100%) was dependent on the magnitude/direction of effects and statistical significance of heterogeneity (28). Given the problems associated with applying statistical tests to assess small sample bias ("publication bias") in meta-analyses with binary outcomes, particularly when significant heterogeneity is present (29), small sample bias was assessed visually by means of a funnel plot for analyses with 10 or more effect sizes.

RESULTS

Search Results

Thirty publications (4, 8, 9, 18-22, 30-51) yielding 31 studies and 107 effect sizes, met inclusion criteria (see Figure 1). This included one study originally published as conference abstract [(18) later withdrawn as the author was unable to attend], but for which statistical outputs for all analyses were kindly provided by the study author. Study details are provided in

Table 1; the total number of individuals included across all studies was 25,041,429. Quality rating scores ranged from 2-8 (mean \pm SD: 5.06 \pm 1.29).

[Insert Figure 1 here]

[Insert Table 1 here]

Global Association between Autoimmune Disorders and Psychosis

An analysis was first conducted to test the global association between all NNAI disorders, excluding rheumatoid arthritis, and psychosis. As shown in Figure 2, a significant positive association was observed (OR = 1.26; 95% CI: 1.12 to 1.41); however, considerable between-study heterogeneity was detected (see Table 2). The funnel plot (Supplementary Figure S1, Panel A) showed no evidence of asymmetry.

[Insert Figure 2 here]

[Insert Table 2 here]

Stratification by Temporal Relationship

The temporal association between NNAI autoimmune disorders (excluding rheumatoid arthritis) and psychosis was investigated by conducting separate meta-analyses for studies examining the comorbidity of these disorders (type A), studies in which the autoimmune disorder preceded psychosis (type B), and studies in which psychosis preceded the autoimmune disorder (type C). Significant positive associations were observed for all three study types: A (OR = 1.20; 95% CI: 1.06 to 1.35), B (OR = 1.43; 95% CI: 1.04 to 1.95), C (OR = 1.55; 95% CI: 1.01 to 2.38) although there was considerable heterogeneity between studies within each type (Table 2).

Stratification by Psychiatric Outcome

Of the 90 effect sizes included in the main analysis (i.e., excluding rheumatoid arthritis), 77 examined schizophrenia, 8 a more broadly defined psychosis outcome that included schizophrenia, and 5 non-schizophrenia psychosis. As shown in Table 2, odds ratios were positive and statistically significant for all three psychiatric diagnostic outcomes: schizophrenia (OR = 1.21, 95% CI: 1.04 to 1.40), broadly-defined psychosis (OR = 1.81, 95% CI: 1.39 to 2.37), non-schizophrenia psychosis (OR = 1.38, 95% CI: 1.01 to 1.88). However, heterogeneity was considerable for all three outcomes.

Stratification by Autoimmune Disorder

Separate meta-analyses were conducted for individual autoimmune disorders where more than three effect sizes were available for analysis (Table 2). A significant positive association was observed for pemphigoid (OR = 1.90, 95% CI: 1.62 to 2.24), pernicious anaemia (OR = 1.91, 95% CI: 1.29 to 2.84), psoriasis (OR = 1.70, 95% CI: 1.51 to 1.91), coeliac disease (OR = 1.53; 95% CI: 1.12 to 2.10), and Graves' disease (OR = 1.33, 95% CI: 1.03 to 1.72). Significant negative associations with psychosis were observed for both ankylosing spondylitis (OR = 0.72, 95% CI: 0.54 to 0.98) and rheumatoid arthritis (OR = 0.65, 95% CI: 0.50 to 0.84, see Figure 3). No significant associations with psychosis were observed for alopecia areata, Crohn's disease, polymyalgia rheumatica, systemic lupus erythematosus (SLE), type 1 diabetes, or ulcerative colitis. Of the seven autoimmune disorders significantly associated with psychosis, heterogeneity estimates were possibly unimportant-to-moderate, and not statistically significant, for pernicious anaemia, ankylosing spondylitis, coeliac disease, Graves' disease, and pemphigoid, whilst significant, moderate-to-substantial heterogeneity was detected for psoriasis and rheumatoid arthritis (Table 2). Visual inspection of the funnel plot for rheumatoid arthritis indicated no substantial asymmetry (Supplementary Figure S1, Panel B).

[Insert Figure 3 here]

DISCUSSION

This is the first meta-analysis to examine the association between multiple non-neurological autoimmune disorders and psychosis. Our primary analysis (which excluded rheumatoid arthritis), showed evidence of a generic, positive association between NNAI disorders and psychosis. Whilst the overall effect size was small ($OR = 1.26$), and substantial heterogeneity was detected, this positive association was consistent across study designs and psychiatric outcomes. Analyses conducted for separate NNAI disorders showed significant, positive associations for pernicious anaemia, pemphigoid, psoriasis, coeliac disease, and Graves' disease, and significant negative associations for ankylosing spondylitis and rheumatoid arthritis.

Stratified analyses demonstrated that not only is there increased comorbidity between NNAI disorders and psychosis (type A), but that NNAI disorders increase the risk for subsequent psychosis (type B) and vice versa (type C). Similarly, the positive association we observed was consistent across psychiatric diagnoses, despite the fact that analyses performed in these subgroups were likely underpowered. However, heterogeneity was not improved when we stratified by these variables, which likely reflects the wide range of NNAI disorders examined. Stratification by NNAI disorder improved heterogeneity estimates for some conditions but not others (alopecia areata, Crohn's disease, psoriasis, rheumatoid arthritis, SLE, and type 1 diabetes). Study factors (e.g., country and data source) and participant factors (sex and treatment) may contribute to the residual heterogeneity observed within these NNAI disorders.

Our analyses were restricted to studies which provided raw data that could be used to calculate odds ratios, thereby precluding us from including data from two nationwide studies, each examining multiple NNAI disorders, that specifically addressed temporal effects (7, 23).

Benros and colleagues reported that the presence of any prior autoimmune disorder increased the risk of schizophrenia by 1.29 fold (7), whilst schizophrenia increased the risk for subsequent autoimmune disorder by 1.53 fold (23). As these results are consistent with the summary odds ratios that we derived from type B (OR = 1.43) and type C (OR = 1.55) studies, it is unlikely that these data would have altered the significant positive associations that we observed, although the statistical significance of our type C analyses (which were likely underpowered) may have increased.

Multiple factors have been suggested to underlie the observed association between NNAI and psychosis, including inflammation, shared genetic vulnerability, predisposing infections, and brain-reactive antibodies (10). Several lines of evidence support the inflammatory hypothesis of psychosis. First, elevated levels of inflammatory markers (i.e., C-reactive protein and cytokines) and proinflammatory cells (e.g., T helper cells 17: Th17) have been observed among individuals with schizophrenia (52-57). Second, increased activity of the complement system has been reported in both schizophrenia (58) and autoimmune disorders (59). Finally, proinflammatory cytokines have been associated with smaller hippocampal volume in first-episode psychosis patients (60) and shown to predict progressive thinning of the prefrontal cortex among individuals at clinical high-risk (CHR) for psychosis (i.e., those thought to be in the putatively prodromal phase of illness based on their clinical presentation) which was in turn associated with transition to psychosis (61). Although activation of the immune system is a core feature of all autoimmune disorders, differences in the downstream molecular immune pathways activated across the different autoimmune diseases may partly explain why we observed significant associations for some, but not all, NNAI disorders in stratified analyses.

That there might be a shared genetic link between autoimmune disorders and psychosis is supported by genome-wide association studies (GWAS) showing that immune regulatory genes

are significantly associated with schizophrenia (62). Of particular relevance is the human leukocyte antigen (HLA) gene loci, which encodes molecules involved in antigen presentation, inflammation, the complement system, and immune responses (63), and has been associated with schizophrenia in numerous GWAS studies (64). However, two recent GWAS studies failed to show that single nucleotide polymorphisms (SNPs) associated with autoimmune disorders (including ankylosing spondylitis, coeliac disease, Graves' disease, psoriasis, and rheumatoid arthritis) were enriched in schizophrenia (65, 66). In contrast, recent studies have reported a significant negative SNP-genetic correlation between schizophrenia and seropositive cases of rheumatoid arthritis (67) and have identified SNPs with potential pleiotropic effects for schizophrenia and rheumatoid arthritis (i.e., where allelic variants of the same gene increase the risk for different disorders) (68). Thus, shared genes (particularly HLA genes) might explain the negative associations we observed between psychosis and rheumatoid arthritis, but not the positive associations we found with other NNAI disorders or the negative association with ankylosing spondylitis.

Infectious diseases are thought to play a role in the aetiology of autoimmune disorders (69). A recent study from Denmark indicated that severe infections resulting in hospitalisation (including bacterial, viral, and other causes of infection) increase the risk for many autoimmune disorders, including, anaemia, coeliac disease, pemphigoid, psoriasis, and rheumatoid arthritis (70). Moreover, data from the same population shows that the risk of schizophrenia is even higher among those exposed to both an autoimmune disorder and serious infection (7). Thus, prior infection could increase the risk for both NNAI disorders and psychosis. However, evidence regarding the role of specific pathogens in NNAI disorders is often lacking, and it is possible that HLA genes [which have been associated with risk of developing both infections and autoimmune diseases (63)] might explain these associations. Moreover, infection is associated with elevated

risk of ankylosing spondylitis and rheumatoid arthritis (70), which in the current study, were negatively associated with psychosis. Thus, infection is unlikely to fully explain the observed pattern of results.

There is current interest in the role of neuronal surface autoantibodies (NSAbs) in psychosis (71). These antibodies (most of which have been only recently characterised) can induce autoimmune encephalopathies, in which psychotic symptoms frequently feature. Antibodies directed against the anti-*N*-methyl-D-aspartate (NMDA) receptor are of particular interest given the links between this receptor and psychosis, with a recent meta-analysis finding that these NSAbs are more commonly detected among individuals with psychosis relative to healthy controls (72). Given that studies of NSAbs are in their infancy, the extent to which they might explain the association between autoimmune disorders and psychosis is unclear, particularly because no studies to date have examined the prevalence of these antibodies in individuals with NNAI disorders. However, encephalopathy associated with autoimmune thyroid disease [also known as Hashimoto's encephalopathy or steroid-responsive encephalopathy associated with autoimmune thyroid disease (SREAT)], a condition associated with neurological and psychiatric symptoms, has been observed among individuals with Graves' disease, all of whom presented with anti-thyroid antibodies (73). Moreover, a recent study reported that anti-thyroid antibodies were present in 13% of patients with schizophreniform disorder (74). Further research is needed to determine the extent to which specific autoantibodies might mediate the association between the specific NNAI disorders and psychosis that we observed.

The potential contribution of corticosteroid treatments to the association between NNAI disorders and psychosis has received relatively little attention. This is surprising given that there is robust evidence of glucocorticoid (i.e., cortisol) abnormalities among individuals with, and at-risk for, psychosis (75). Moreover, a recent population-based study reported increased risks for

schizophrenia spectrum disorders among children/adolescents exposed to glucocorticoid treatment (76). Of particular relevance to our findings, corticosteroids are among the most common treatment types for psoriasis and pemphigoid (77-79), and some forms of autoimmune anaemia (80). However, corticosteroids are commonly used in the treatment of rheumatoid arthritis (81), which was negatively associated with psychosis. Thus, the contribution of corticosteroids to these associations is currently unclear.

The negative association we observed between rheumatoid arthritis and psychosis is consistent with an earlier meta-analysis (82). Given the late age-of-onset for rheumatoid arthritis, it is possible that this relationship is partly explained by reduced life expectancy and poorer healthcare (leading to lower detection rates) among people with psychosis. Of note, rates of cancer, a disease which typically onsets in later life, are also lower among individuals with psychosis (83). Consistent with this explanation, juvenile-onset rheumatoid arthritis was not significantly associated with psychosis (see Figure 3), although juvenile- and late-onset forms differ with regards to symptom severity and treatment (84). Moreover, the fact that significant negative associations were found across type A (8, 18, 44), B (41, 47), and C (20) studies is at odds with this hypothesis, and instead suggests that a third factor (e.g., genetic influences or treatment) may underlie this association.

One novel finding was the significant negative association observed between ankylosing spondylitis and psychosis. Whilst this result is perhaps unsurprising given that ankylosing spondylitis was initially thought to be a type of rheumatoid arthritis, the aetiology and presentation of these conditions differ substantially (85). Specifically, the age of onset is far earlier for ankylosing spondylitis than for rheumatoid arthritis, the former is more common in males whilst the reverse is true for rheumatoid arthritis, and the disorders are associated with different HLA genes (86). Further investigation is needed to identify factors (including other

polygenes) common to both disorders that might explain their negative association with psychosis. As a related issue, it is interesting to note that we observed positive associations with NNAI disorders that are traditionally classified as organ-specific (pernicious anaemia, Graves' disease, pemphigoid, and psoriasis), but negative associations with systemic NNAI disorders (ankylosing spondylitis and rheumatoid arthritis) which target multiple organs. However, the distinction between organ-specific and systemic disorders is not clear cut, and current categorisation is largely based on clinical presentation as opposed to the expression pattern of the self-antigen (87).

Whilst psychotic symptoms are a common neuropsychiatric feature of SLE (88), SLE was not significantly associated with psychosis in this meta-analysis; in fact, only one study meeting inclusion criteria reported a significant positive association for SLE and psychosis (48). This may be because 'psychoses' or 'psychotic manifestations' in SLE can be acute and transient, and therefore not equivalent to a diagnosis of psychotic disorder. In addition, those studies which do refer to diagnosed psychotic disorders in SLE are often isolated case reports (89) or studies which do not include control groups (90), which were not examined in this meta-analysis.

Strengths and Limitations

The vast quantity of data examined (> 25 million individuals) is a major strength of this study. Our search strategy was conducted to ensure that we captured all relevant studies, including some very early publications. A further strength relates to the fact that we systematically investigated the effect of temporality, psychiatric diagnosis, and specific NNAI disorders on the magnitude and consistency of effects.

Some limitations must be noted. First, due to substantial variation in the effect size measures reported across studies, we extracted raw data to compute odds ratios. This meant

that our effect sizes were not adjusted for important confounding factors that may have influenced the association. However, half of the included studies matched cases and controls on age and sex (Table 1). Second, as we were keen to utilise all available data, we included studies utilising both small clinical samples and large nationwide populations, which may have contributed to heterogeneity. Third, as this study was undertaken for as partial fulfilment of a Master's thesis (S.H.), a protocol was not published prior to undertaking the study, as such our analysis strategy may have been driven by the data. Fourth, by extracting (and pooling) data for individual NNAI disorders, patients with more than one NNAI disorder may have been counted twice in the primary (overall) analysis. Fifth, we examined a wide range of disorders classified as 'autoimmune' in the primary papers which included some diseases for which an autoimmune basis has not yet been demonstrated. However, to increase validity, we included only NNAI disorders were listed as such by the American Autoimmune and Related Diseases Association. Finally, despite efforts to obtain data from study authors for all eligible studies, we were unable to include data from two large, nationwide studies (7, 23). However, as noted above, it is unlikely that including these data would have substantially altered the overall finding.

Implications

The finding that psychosis is associated with NNAI disorders (i.e., those which would not be expected to directly target the brain, but nonetheless generate substantial immune system activation in the peripheral systems that might ultimately affect the brain) is particularly important. However, given the range of possible mechanisms that may underlie the significant associations that we observed, the considerable heterogeneity across studies, and the fact that all effect sizes were small, treatment recommendations based on these findings would be premature. Regardless of the mechanism, these findings suggest that careful monitoring of

individuals with specific autoimmune diseases (particularly anaemia, Graves' disease, and pemphigoid, as these were the most consistent effects) for early signs of psychosis is warranted.

With regards to future research, we recommend that (1) studies are designed to better disentangle the temporal nature of the association between NNAI disorders and psychosis as such studies have demonstrated that both psychosis (7, 23) and depression (91) show bidirectional associations with autoimmune disorders; (2) larger studies are undertaken to examine the presence of neuronal surface autoantibodies among individuals with psychosis; (3) greater efforts are made in large cohort studies to include information on potential confounders such as socioeconomic status, adversity, and tobacco use; and (4) studies are undertaken to evaluate the effect of corticosteroid treatment on the relationship between NNAI disorders and psychosis.

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CONFLICT OF INTEREST DISCLOSURES

Professor Murray has received honoraria from Janssen, Astra-Zeneca, Lilly, BMS. All other authors report no biomedical financial interests or potential conflicts of interests.

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FIGURE CAPTIONS

Figure 1. Search Process

Figure 2. Results of Overall Meta-Analysis for all Non-Neurological Autoimmune Disorders (Except Rheumatoid Arthritis) and Psychosis

Figure 3. Results of Meta-Analysis for Rheumatoid Arthritis and Psychosis

FIGURE LEGENDS

Figure 1. Overview of the review process and exclusion reasons.

Figure 2. Abbreviations: SZ: schizophrenia; PY: psychosis; NSP: non-schizophrenia psychosis; AI: autoimmune; Diag: psychiatric diagnosis; HSV: Hypersensitivity vasculitis; SLE: Systemic lupus erythematosus; OR: odds ratio; CI: confidence interval. ^a autoimmune haemolytic type; ^b hereditary haemolytic type; ^c pernicious type; ^d acquired haemolytic; ^e other hereditary haemolytic type; ^f childhood-onset. Marker and line colours indicate study design: type A (red), type B (blue), type C (pink).

Figure 3. Abbreviations: OR: odds ratio; CI: confidence interval. All studies examine schizophrenia with the following exceptions: Allebeck et al (1985, second row) (30): non-schizophrenia psychosis; Sundquist et al (2008, first row) (47): non-schizophrenia psychosis; Rothermich & Phillips (1963) (44): broadly defined psychosis. Specific rheumatoid arthritis subtypes are as follows: Chen et al (2012, second row) (8): juvenile-onset; Eaton et al (2006, second row) (9): seropositive; Mors et al (1999, second row) (41): juvenile-onset. Marker and line colours indicate study design: type A (red), type B (blue), type C (pink).

Table 1. Details and Quality Rating for Studies Meeting Inclusion Criteria

Author	Type ^a	Psychiatric diagnosis (measure)	Autoimmune disorder (measure)	Country	Design (E - O) ^b	Data source	Sample	Age ^c (yrs)	Male (%)	Matching factors	Outcome measure	Quality score (max 8)
Allebeck <i>et al.</i> 1985 (30)	C	Schizophrenia and Affective Psychosis (ICD-7)	Rheumatoid arthritis (ICD-7)	Sweden	Cohort (PSY - AI)	County inpatient register	Sz/Psy (N=1,811) Cont (N=16,617)	NS	39.4	None	Incidence	5
Butwicka <i>et al.</i> 2015 (31)	B	Psychosis (ICD-8, ICD-9, ICD-10)	Childhood onset Type 1 Diabetes (ICD-8, ICD-9)	Sweden	Cohort (AI - PSY)	National diabetes register	AI (N=17,122) Cont (N=1,696,611)	AI: 9.3 C: NS	AI: 54.1 C: 53.9	Age, sex, country of birth	Incidence	6
Butwicka <i>et al.</i> 2017 Part A/B (22)	B/C	Psychosis (ICD-8, ICD-9, ICD-10)	Childhood onset Coeliac disease (Biopsy)	Sweden	A: Cohort (AI - PSY) B: Case control (PSY - AI)	Histological data and National patient register	AI (N=10,903) Cont (N=1,042,072)	NS	AI: 37.3 C: 38.8	Age, sex, country of birth	Incidence / Prevalence	6/6
Chen <i>et al.</i> 2011 (32)	C	Schizophrenia (ICD-9)	Pemphigoid (ICD-9)	Taiwan	Case control (PSY - AI)	National health insurance database	AI (N=3,485) Cont (N=17,425)	AI: 74.0 C: 74.0	AI: 54.8 C: 54.8	Age, sex	Prevalence	6
Chen <i>et al.</i> 2012 (8)	A	Schizophrenia (ICD-9)	All NNAI (N=25) (ICD-9)	Taiwan	Case control (AI - PSY)	National health insurance database	Sz (N=10,811) Cont (N=108,110)	NS	Sz: 54.9 C: 49.5	Age	Prevalence	5
Chu <i>et al.</i> 2012 (33)	A	Schizophrenia (ICD-9)	Alopecia areata (ICD-9)	Taiwan	Case control (PSY - AI)	National health insurance database	AI (N=5,117) Cont (N=20,468)	NS	AI: 50.8 C: 50.8	Age, sex	Prevalence	5

Author	Type ^a	Psychiatric diagnosis (measure)	Autoimmune disorder (measure)	Country	Design (E - O) ^b	Data source	Sample	Age ^c (yrs)	Male (%)	Matching factors	Outcome measure	Quality score (max 8)
Cremaschi <i>et al.</i> 2017 (34)	A	Schizophrenia (NS)	All NNAI (N=6) (NS)	Sweden	Case control (PSY - AI)	Hospital discharge register and patient interview	Sz (N=5,278) Cont (N=6,485)	Sz: 53.9 C: 56.3	Sz: 59.7 C: 51.2	None	Prevalence	3
Eaton <i>et al.</i> 2006 (9)	B	Schizophrenia (ICD-8, ICD-10)	All NNAI (N=24) (ICD-8, ICD-10)	Denmark	Case control (AI - PSY)	National psychiatric and patient register	Sz (N=7,704) Cont (N=192,590)	NS	Sz: 66.0 C: 66.0	Age, sex	Prevalence	5
Forsti <i>et al.</i> 2016 Part A/B (35)	B/C	Schizophrenia (ICD-9, ICD-10)	Pemphigoid (ICD-9, ICD-10)	Finland	A: Cohort (AI - PSY) B: Case control (PSY - AI)	National register for healthcare	AI (N=4,524) Cont (N=66,138)	AI: 77.0 C: 73.0	AI: 40.0 C: 45.0	None	Incidence/ Prevalence	5/5
Guerin <i>et al.</i> 2012 (19)	A	Psychosis (ICD-9)	Psoriasis (ICD-9)	USA	Case control (PSY - AI)	National health insurance database	AI (N=106,128) Cont (N=106,128)	AI: 52.1 C: 52.1	AI: 48.5 C: 48.5	Age, sex	Prevalence	5
Huilaja <i>et al.</i> 2018 (36)	A	Psychosis (ICD-9, ICD-10)	Dermatological NNAI (N=2) (ICD-9, ICD-10)	Finland	Case control (PSY - AI)	National register for healthcare	AI (N=21,690) Cont (N=17,488)	AI: 41.2 C: 40.5	AI: 41.5 C: 41.3	Age, sex	Prevalence	5
Hutchinson <i>et al.</i> 1996 (4)	A	Psychosis (DSM-III)	Systemic lupus erythematosus (NS)	Trinidad	Case control (PSY - AI)	Outpatient sample	AI (N=45) Cont (N=48)	NS	NS	None	Prevalence	-
Juvonen <i>et al.</i> 2007 (37)	B	Schizophrenia (ICD-8, DSM-III-R)	Type 1 Diabetes (NS)	Finland	Cohort (AI - PSY)	National population register	Entire population (N=896,175)	NS	NS	None	Incidence	5

Author	Type ^a	Psychiatric diagnosis (measure)	Autoimmune disorder (measure)	Country	Design (E - O) ^b	Data source	Sample	Age ^c (yrs)	Male (%)	Matching factors	Outcome measure	Quality score (max 8)
Kridin <i>et al.</i> 2017 (38)	A	Schizophrenia (NS)	Pemphigoid (NS)	Israel	Case control (PSY - AI)	Health services database	AI (N=1,985) Cont (N=9,874)	AI: 72.1 C: 72.1	AI: 40.2 C: 40.1	Age, sex, ethnicity	Prevalence	3
Lauerma <i>et al.</i> 1998 Part A (39)	B	Schizophrenia (DSM-III-R)	Rheumatoid arthritis (NS)	Finland	Cohort (AI - PSY)	National hospital discharge database	AI (N=5,626) Cont (N=5,330)	NS	NS	None	Incidence	4
Lauerma <i>et al.</i> 1998 Part B (39)	A	Schizophrenia (DSM-III-R)	Rheumatoid arthritis (NS)	Northern Finland	Cross sectional (AI - PSY)	National hospital discharge database	Sz (N76) Cont (N=10,503)	NS	NS	None	Prevalence	3
Ludvigsson <i>et al.</i> 2007 (40)	B	Schizophrenia and Non-Affective Psychosis (ICD-8, ICD-9, ICD-10)	Coeliac disease (ICD-7, ICD-8, ICD-9, ICD-10)	Sweden	Cohort (AI - PSY)	National inpatient register	AI (N=14,003) Cont (N=68,125)	NS	Sz: 41.1 C: 41.0	Age, sex, area of residence	Incidence	7
Marrie <i>et al.</i> 2018 (21)	A	Schizophrenia (ICD-9, ICD-10)	Rheumatoid arthritis (ICD-9, ICD-10)	Canada	Case control (PSY - AI)	National health database	AI (N=6,350) Cont (N=33,584)	AI: 53.7 C: 53.7	AI: 27.8 C: 27.8	Age, sex, geographic region	Prevalence	8
Mors <i>et al.</i> 1999 (41)	B	Schizophrenia (ICD-8)	Rheumatoid arthritis (adult and juvenile) (ICD-8)	Denmark	Case control (AI - PSY)	National psychiatric and patient register	Sz (N=20,495) Cont (N=204,912)	NS	Sz: 57.6 C: 57.6	Age, sex	Prevalence	5

Author	Type ^a	Psychiatric diagnosis (measure)	Autoimmune disorder (measure)	Country	Design (E - O) ^b	Data source	Sample	Age ^c (yrs)	Male (%)	Matching factors	Outcome measure	Quality score (max 8)
Petrak <i>et al.</i> 2003 (42)	C	Possible Psychosis (DSM-IV)	Type 1 Diabetes (NS)	Germany	Case control (PSY - AI)	Inpatient sample (cases) and general population (controls)	AI (N=313) Cont (N=2,046)	AI: 28.3 C: 30.2	AI: 62.3 C: 50.8	None	Prevalence	4
Rajkumar <i>et al.</i> 2017 (43)	A	Schizophrenia (ICD-8, ICD-10)	Type 1 Diabetes (ICD-8, ICD-10)	Denmark	Cohort (PSY - AI)	National patient registers and prescription registry	Sz (N=8,945) Cont (N=2,727,565)	NS	Sz: 59.7 C: 50.8	None	Incidence	5
Rothermich & Philips 1963 (44)	A	Psychosis (NS)	Rheumatoid arthritis (NS)	USA	Case control (AI - PSY)	Hospital records with AI screening	Psy (N=16,000) Cont (N=4,040)	NS	NS	None	Prevalence	2
Schmitt & Ford 2010 (45)	A	Schizophrenia (ICD-10)	Psoriasis (ICD-10)	Germany	Case control (PSY - AI)	Outpatient records database	AI (N=3,147) Cont (N=3,147)	AI: 57.1 C: 57.1	AI: 44.7 C: 44.7	Age, sex	Prevalence	6
Sellgren <i>et al.</i> 2014 (20)	C	Schizophrenia (ICD-8, ICD-9, ICD-10)	Rheumatoid arthritis and Ankylosing spondylitis (ICD-8, ICD-9, ICD-10)	Sweden	Cohort (PSY - AI)	National population register	Entire population (N=6,413,683)	Sz: 44.0 C: NS	Sz: 59.0 C: NS	None	Incidence	6
Shen <i>et al.</i> 2016 (46)	B	Schizophrenia (ICD-9)	Ankylosing spondylitis (ICD-9)	Taiwan	Cohort (AI - PSY)	National health insurance database	AI (N=2,331) Cont (N=9,324)	AI: 36.5 C: 36.5	AI: 64.9 C: 63.9	Age, sex	Incidence	7

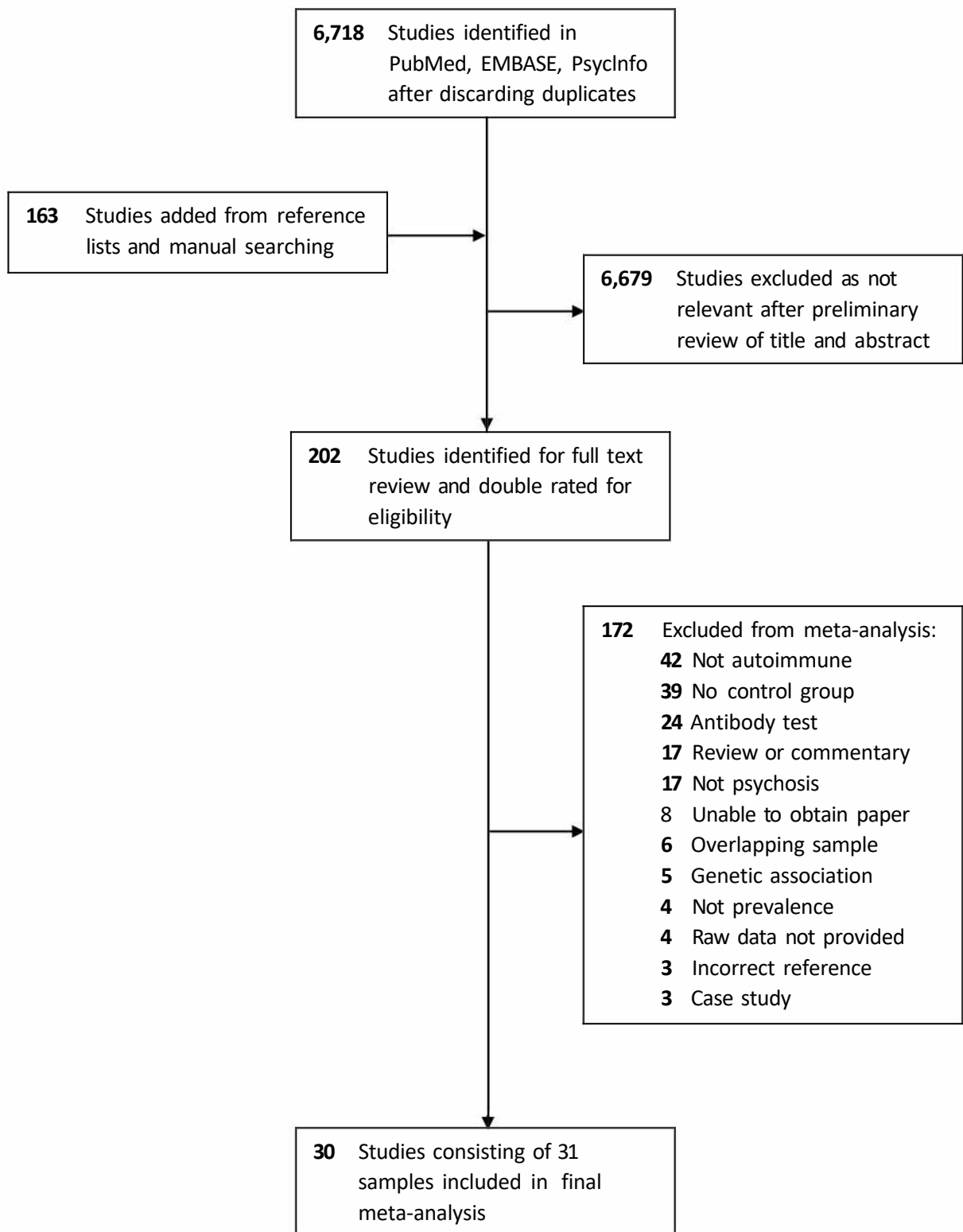
Author	Type ^a	Psychiatric diagnosis (measure)	Autoimmune disorder (measure)	Country	Design (E - O) ^b	Data source	Sample	Age ^c (yrs)	Male (%)	Matching factors	Outcome measure	Quality score (max 8)
Sundquist <i>et al.</i> 2008 (47)	B	Schizophrenia and Psychosis (ICD-8, ICD-9, ICD-10)	Rheumatic AI (N=3) (ICD-8, ICD-9, ICD-10)	Sweden	Cohort (AI - PSY)	National hospital discharge register	Entire population (N=8,142,857 ^d)	NS	NS	None	Incidence	6
Tiosano <i>et al.</i> 2017 (48)	A	Schizophrenia (NS)	Systemic lupus erythematosus (NS)	Israel	Case control (PSY - AI)	Health services database	AI (N=5,018) Cont (N=25,090)	AI: 50.2 C: 50.2	AI: 18.0 C: 18.0	Age, sex	Prevalence	3
Tu <i>et al.</i> 2017 (49)	A	Schizophrenia (ICD-9)	Psoriasis (ICD-9)	Taiwan	Cross sectional (AI - PSY)	National health insurance database	AI (N=10,796) Cont (N=767,327)	AI: 50.5 C: 45.9	AI: 55.2 C: 48.4	None	Prevalence	6
Weber <i>et al.</i> 2013 (18)	A	Schizophrenia (ICD-9)	All NNAI (N=9) (ICD-9)	USA	Cross sectional (AI - PSY)	Hospital discharge database	Entire sample (N=2,875,233)	NS	NS	None	Prevalence	5
West <i>et al.</i> 2006 (50)	A	Schizophrenia (NS)	Gastro-intestinal AI (N=3) (NS)	UK	Case control (PSY - AI)	Primary care database	AI (N=18,994) Cont (N=95,052)	NS	NS	Age, sex, GP, FU time	Prevalence	5
Yu <i>et al.</i> 2017 (51)	C	Schizophrenia (ICD-9)	Psoriasis (ICD-9)	Taiwan	Cohort (PSY - AI)	National health insurance database	Sz(N=4,980) Cont (N=19,920)	Sz: 46.5 C: 46.6	Sz: 50.7 C: 50.7	Age, sex	Incidence	5

Note. NNAI: non-neurological autoimmune disorders; AI: autoimmune disorder; PSY: psychiatric disorder; Sz: schizophrenia; Psy: psychosis; Cont/C: control group. ICD: International Classification of Disease; DSM: Diagnostic and Statistical Manual of Mental Disorders; USA: United States of America; UK: United Kingdom; GP: general practitioner; FU: follow-up. ^a Type: A: comorbidity of schizophrenia/psychosis and autoimmune; B: autoimmune precedes schizophrenia/psychosis; C: schizophrenia/psychosis precedes autoimmune; ^b Study design: E: exposure; O: outcome; ^c Age: mean or median.

Table 2. Results of Meta-Analyses Examining Associations between Non-Neurological Autoimmune Disorders and Psychosis

Analysis	No. studies (type)	No. effect sizes (diagnosis)	Total N (PSY/AI)	OR	(95% CI)	<i>p</i>	Q (<i>p</i>)	<i>I</i> ²	(95% CI)
Overall ^a	27 (A=13; B=8; C=6)	90 (SZ=77; PY=8; NSP=5)	641613 / 540349	1.26	(1.12 to 1.41)	<0.001	<0.001	88.08	(85.94 to 89.89)
Temporal relationship ^a									
Comorbidity (A)	7 (A=13)	49 (SZ=45; PY=4)	410627 / 328199	1.20	(1.06 to 1.35)	0.003	<0.001	84.80	(80.67 to 88.04)
PSY precedes AI (B)	6 (B=8)	34 (SZ=28; PY=2; NSP=4)	193594 / 176578	1.43	(1.04 to 1.95)	0.03	<0.001	88.58	(85.10 to 91.25)
AI precedes PSY (C)	3 (C=6)	7 (SZ=4; PY=2; NSP=1)	37392 / 35572	1.55	(1.01 to 2.38)	0.046	<0.001	87.14	(75.77 to 93.18)
Psychiatric diagnosis ^a									
Schizophrenia	20 (A=10; B=6; C=4)	77 (SZ=77)	615498 / 290506	1.21	(1.04 to 1.40)	0.01	<0.001	87.08	(84.50 to 89.23)
Psychosis (broadly defined)	7 (A=3; B=2; C=2)	8 (PY=8)	14241 / 167104	1.81	(1.39 to 2.37)	<0.001	<0.001	85.60	(73.58 to 92.16)
Non-schizophrenia psychosis	4 (B=3; C=1)	5 (NSP=5)	11874 / 82739	1.38	(1.01 to 1.88)	0.046	0.003	75.34	(39.36 to 89.97)
Autoimmune disorder									
Alopecia areata	3 (A=2; B=1)	3 (SZ=3)	18777 / 5283	0.90	(0.38 to 2.10)	0.80	0.010	78.26	(29.97 to 93.25)
Anaemia (pernicious)	3 (A=2; B=1)	3 (SZ=3)	32239 / 1009	1.91	(1.29 to 2.84)	0.001	0.61	0.00	(0.00 to 93.12)
Ankylosing spondylitis	6 (A=2; B=3; C=1)	7 (SZ=6; NSP=1)	73967 / 63198	0.72	(0.54 to 0.98)	0.04	0.14	37.54	(0.00 to 73.70)
Coeliac disease	6 (A=2; B=3; C=1)	7 (SZ=4; PY=2; NSP=1)	19507 / 54624	1.53	(1.12 to 2.10)	0.008	0.131	39.08	(0.00 to 74.38)
Crohn's disease	4 (A=3; B=1)	4 (SZ=4)	32364 / 20907	0.67	(0.34 to 1.30)	0.23	0.002	79.97	(46.98 to 92.44)
Graves' disease	3 (A=2; B=1)	3 (SZ=3)	32239 / 7799	1.33	(1.03 to 1.72)	0.03	0.18	41.19	(0.00 to 82.07)
Pemphigoid	6 (A=2; B=2; C=2)	8 (SZ=6; NSP=2)	20232 / 23585	1.90	(1.62 to 2.24)	<0.001	0.322	13.81	(0.00 to 56.59)
Polymyalgia rheumatica	3 (A=2; B=1)	3 (SZ=3)	23354 / 112	1.63	0.41 to 6.48)	0.49	0.030	71.35	(2.74 to 91.56)
Psoriasis	8 (A=6; B=1; C=1)	8 (SZ=6; PY=2)	54578 / 141673	1.70	(1.51 to 1.91)	<0.001	0.010	61.94	(17.82 to 82.38)
Rheumatoid arthritis	12 (A=6; B=4; C=2)	17 (SZ=14; PY=1; NSP=2)	244320 / 125090	0.65	(0.50 to 0.84)	0.001	<0.001	79.28	(67.52 to 86.79)
SLE	7 (A=5; B=2)	8 (SZ=6; PY=1; NSP=1)	48140 / 66545	0.95	(0.65 to 1.39)	0.80	<0.001	76.91	(54.10 to 88.39)
Type 1 Diabetes	8 (A=4; B=3; C=1)	8 (SZ=6; PY=2)	47208 / 132921	0.79	(0.43 to 1.46)	0.46	<0.001	97.31	(96.10 to 98.14)
Ulcerative colitis	4 (A=3; B=1)	4 (SZ=4)	32420 / 15526	1.04	(0.69 to 1.56)	0.86	0.08	56.20	(0.00 to 85.48)

Note. ^a Effect sizes for rheumatoid arthritis excluded from analyses. Temporal relationship group: A: comorbidity of schizophrenia/psychosis and autoimmune; B: autoimmune diagnosis precedes schizophrenia/psychosis; C: schizophrenia/psychosis diagnosis precedes autoimmune. PSY: psychosis; AI: autoimmune disorder; SLE: systemic lupus erythematosus; OR: odds ratio; CI: confidence interval; Q: Q statistic from heterogeneity analysis; *I*²: *I* squared statistic from heterogeneity analysis. Bold indicates statistical significance at the 0.05 level (2-tailed).



Author	AI Disorder [Diag]	OR [95% CI]
Chen et al (2012) (8)	Alopecia areata [SZ]	0.54 [0.22-1.32]
Chen et al (2012) (8)	Anaemia [a] [SZ]	0.71 [0.09-5.43]
Chen et al (2012) (8)	Anaemia [b] [SZ]	1.43 [0.86-2.38]
Chen et al (2012) (8)	Anaemia [c] [SZ]	2.06 [1.30-3.26]
Chen et al (2012) (8)	Ankylosing spondylitis [SZ]	0.72 [0.50-1.06]
Chen et al (2012) (8)	Arteritis obliterans [SZ]	10.00 [0.20-504.01]
Chen et al (2012) (8)	Coeliac disease [SZ]	2.20 [1.07-4.52]
Chen et al (2012) (8)	Crohn's disease [SZ]	0.01 [0.00-0.09]
Chen et al (2012) (8)	Goodpasture syndrome [SZ]	10.00 [0.20-504.01]
Chen et al (2012) (8)	Graves disease [SZ]	1.17 [0.94-1.45]
Chen et al (2012) (8)	Hashimoto's thyroiditis [SZ]	0.51 [0.19-1.40]
Chen et al (2012) (8)	Hypersensitivity vasculitis [SZ]	5.34 [2.26-12.59]
Chen et al (2012) (8)	Kawasaki disease [SZ]	0.53 [0.03-9.04]
Chen et al (2012) (8)	Pemphigoid [SZ]	0.91 [0.05-16.44]
Chen et al (2012) (8)	Polyarteritis nodosa [SZ]	2.08 [1.05-4.12]
Chen et al (2012) (8)	Polymyalgia rheumatica [SZ]	0.71 [0.29-1.77]
Chen et al (2012) (8)	Psoriasis [SZ]	1.80 [1.36-2.40]
Chen et al (2012) (8)	SLE [SZ]	0.94 [0.52-1.69]
Chen et al (2012) (8)	Systemic sclerosis [SZ]	0.40 [0.02-6.76]
Chen et al (2012) (8)	Thromboangiitis obliterans [SZ]	2.09 [0.10-41.66]
Chen et al (2012) (8)	Type 1 Diabetes [SZ]	1.77 [1.21-2.60]
Chen et al (2012) (8)	Ulcerative colitis [SZ]	1.33 [0.30-5.83]
Chen et al (2012) (8)	Uveitis [SZ]	0.14 [0.03-0.56]
Chu et al (2012) (33)	Alopecia areata [SZ]	0.61 [0.43-0.88]
Cremašchi et al (2017) (34)	Hyperthyroidism [SZ]	0.59 [0.41-0.86]
Cremašchi et al (2017) (34)	Hypothyroidism [SZ]	1.61 [1.36-1.89]
Cremašchi et al (2017) (34)	Polymyalgia rheumatica [SZ]	1.28 [0.08-20.53]
Cremašchi et al (2017) (34)	SLE [SZ]	0.57 [0.39-0.83]
Cremašchi et al (2017) (34)	Type 1 Diabetes [SZ]	0.95 [0.63-1.45]
Guerin et al (2012) (19)	Psoriasis [PY]	1.57 [1.52-1.64]
Hullaja et al (2018) (36)	Hidradenitis suppurativa [PY]	2.75 [2.30-3.30]
Hullaja et al (2018) (36)	Psoriasis [PY]	1.91 [1.66-2.20]
Hutchinson et al (1996) (4)	SLE [PY]	13.17 [0.71-245.47]
Kridin et al (2017) (38)	Pemphigoid [SZ]	1.54 [1.07-2.21]
Rajkumar et al (2017) (43)	Type 1 Diabetes [SZ]	0.60 [0.37-0.97]
Schmitt & Ford (2010) (45)	Psoriasis [SZ]	0.93 [0.60-1.43]
Tosano et al (2017) (48)	SLE [SZ]	1.68 [1.27-2.20]
Tu et al (2017) (49)	Psoriasis [SZ]	1.78 [1.49-2.14]
Weber et al (2013) (18)	Anaemia [c] [SZ]	1.43 [0.64-3.20]
Weber et al (2013) (18)	Ankylosing spondylitis [SZ]	0.43 [0.11-1.73]
Weber et al (2013) (18)	Crohn's disease [SZ]	0.71 [0.53-0.95]
Weber et al (2013) (18)	Graves disease [SZ]	1.35 [1.01-1.82]
Weber et al (2013) (18)	Psoriasis [SZ]	2.19 [1.59-3.03]
Weber et al (2013) (18)	SLE [SZ]	1.01 [0.79-1.30]
Weber et al (2013) (18)	Type 1 Diabetes [SZ]	1.48 [1.37-1.61]
Weber et al (2013) (18)	Ulcerative colitis [SZ]	1.20 [0.88-1.64]
West et al (2006) (50)	Coeliac disease [SZ]	0.74 [0.40-1.36]
West et al (2006) (50)	Crohn's disease [SZ]	0.73 [0.43-1.24]
West et al (2006) (50)	Ulcerative colitis [SZ]	0.62 [0.39-0.99]
Butwicka et al (2015) (31)	Type 1 Diabetes [I] [PY]	0.88 [0.42-1.85]
Butwicka et al (2017) (22) Part A	Coeliac disease [I] [PY]	1.82 [0.97-3.41]
Eaton et al (2006) (9)	Alopecia areata [SZ]	2.42 [1.05-5.60]
Eaton et al (2006) (9)	Anaemia [d] [SZ]	12.50 [3.13-50.01]
Eaton et al (2006) (9)	Anaemia [e] [SZ]	0.93 [0.13-6.81]
Eaton et al (2006) (9)	Anaemia [c] [SZ]	5.00 [0.24-104.15]
Eaton et al (2006) (9)	Ankylosing spondylitis [SZ]	2.68 [0.81-8.81]
Eaton et al (2006) (9)	Chronic active hepatitis [SZ]	8.34 [2.69-25.86]
Eaton et al (2006) (9)	Coeliac disease [SZ]	3.85 [1.34-11.03]
Eaton et al (2006) (9)	Crohn's disease [SZ]	1.24 [0.71-2.17]
Eaton et al (2006) (9)	Endometriosis [SZ]	0.62 [0.23-1.69]
Eaton et al (2006) (9)	Graves disease [SZ]	2.33 [1.13-4.80]
Eaton et al (2006) (9)	Interstitial cystitis [SZ]	2.13 [1.59-2.86]
Eaton et al (2006) (9)	Mycositis [SZ]	1.95 [1.42-2.68]
Eaton et al (2006) (9)	Other adrenal gland [SZ]	1.32 [0.18-9.83]
Eaton et al (2006) (9)	Pemphigoid [SZ]	1.92 [0.25-14.70]
Eaton et al (2006) (9)	Polymyalgia rheumatica [SZ]	4.17 [1.62-10.75]
Eaton et al (2006) (9)	Psoriasis [SZ]	1.67 [0.40-6.98]
Eaton et al (2006) (9)	Purpura [SZ]	1.39 [0.51-3.80]
Eaton et al (2006) (9)	SLE [SZ]	0.44 [0.03-7.16]
Eaton et al (2006) (9)	Thyroiditis [SZ]	3.33 [0.76-14.58]
Eaton et al (2006) (9)	Type 1 Diabetes [SZ]	0.71 [0.47-1.06]
Eaton et al (2006) (9)	Ulcerative colitis [SZ]	1.42 [0.81-2.48]
Eaton et al (2006) (9)	Uveitis [SZ]	1.39 [0.33-5.77]
Forst et al (2016) (35) Part A	Pemphigoid [NSP]	1.53 [1.07-2.19]
Forst et al (2016) (35) Part A	Pemphigoid [SZ]	1.02 [0.41-2.51]
Juvonen et al (2007) (37)	Type 1 Diabetes [SZ]	0.36 [0.31-0.42]
Ludvigsson et al (2007) (40)	Coeliac disease [NSP]	1.52 [1.12-2.05]
Ludvigsson et al (2007) (40)	Coeliac disease [SZ]	1.36 [0.75-2.47]
Shen et al (2016) (46)	Ankylosing spondylitis [SZ]	1.27 [0.54-2.98]
Sundquist et al (2008) (47)	Ankylosing spondylitis [NSP]	0.67 [0.39-1.16]
Sundquist et al (2008) (47)	Ankylosing spondylitis [SZ]	0.34 [0.13-0.91]
Sundquist et al (2008) (47)	SLE [NSP]	1.17 [0.78-1.76]
Sundquist et al (2008) (47)	SLE [SZ]	0.33 [0.13-0.89]
Butwicka et al (2017) (22) Part D	Coeliac disease [I] [PY]	1.52 [0.81-10.94]
Chen et al (2011) (32)	Pemphigoid [SZ]	2.63 [1.57-4.41]
Forst et al (2016) (35) Part B	Pemphigoid [NSP]	2.05 [1.62-2.59]
Forst et al (2016) (35) Part B	Pemphigoid [SZ]	2.27 [1.70-3.04]
Petrak et al (2003) (42)	Type 1 Diabetes [PY]	0.11 [0.01-1.73]
Sellgren et al (2014) (20)	Ankylosing spondylitis [SZ]	0.64 [0.46-0.89]
Yu et al (2017) (51)	Psoriasis [SZ]	1.63 [1.28-2.07]
Summary		1.26 [1.12-1.41]

